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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

NGUYEN, DAVE TRONG

ART UNIT PAPER NUMBER

1632

DATE MAILED: 09/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/811,323

Applicant(s)

GERMAN ET AL.

Examiner

Dave Nguyen

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-51 is/are pending in the application.
- 4a) Of the above claim(s) 51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-25, 27, 29-33 and 46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____

Applicant's election with traverse of Group I claims, claims 18-50, and of species of capsule and species of antigen in the response filed June 20, 2002 is acknowledged.

Applicant's traversal is that there would be no undue burden to perform a search of all presently pending claims, that a reasonable number of species has been claimed, and that the species restriction is not proper. The traversal is not found persuasive because not only a search of Group I claims do not necessarily overlap with that of Group II claims, Group II claims is directed to a suppository composition wherein the only intended use of the composition is to produce a therapeutic effect in any mammal, and as such, the claimed method of Group II generates distinct function and effect and requires an a further undue burden on the examiner to examine the invention. In addition, not all of the species do not share any substantially common structure, and further, the generic claim embraces an enormous number of combinations of vectors and/or protein encoding DNA, which exhibit distinct function and effect depending on an intended application when read in light of the specification. Thus, a search of all claims in completion would result in an undue burden on the examiner. Therefore, the species restriction is proper and maintained.

Claim 51 has been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 26, 28, 34-45, 47-50 readable on non-elected species have been withdrawn by the examiner.

Claims 18-25, 27, 29-33 and 46 are pending for examination.

For the purpose of a complete examination of all of the outstanding issues embraced by the generic claim insofar as it does not institute an undue burden on the examiner, species of plasma protein, e.g., insulin, as recited in claim 46 has been rejoined to the species examination.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18 and 20, directed specifically to the subject matter as recited in claim 20, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 embraces a genus of altered protein relative to a wild type protein, and yet must exhibit applicant's intended utility, which is for use in a gene therapy protocol for correcting a disease or disorder in a mammal. The as-filed specification at the time the invention was made does not provide a sufficient description of the genus as claimed. An adequate written description of a polypeptide or protein or peptide requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the core structure of the claimed protein or polypeptide sequences itself. It is not sufficient to have a description of a contemplation of claiming such genus of altered or mutant proteins relative to any wild type protein and within the framework of the invention, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of a representative number of species of altered proteins embraced by the genus of altered proteins relative to any wild-type protein, which does not find a sufficient written description from the as-filed specification. Claiming a genus of unspecified protein sequences and that achieve a result as contemplated by the as-filed specification without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Claims 18-25, 27, 29-33 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, because the specification, while being enabling for

A method of delivering a non-therapeutic secreted protein into the bloodstream of a mammalian subject, the method comprising:

Introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a non-therapeutic nucleic acid molecule encoding a secreted protein and a promoter operably linked to the nucleic acid molecule, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject;

A method of inducing an immune response to a secreted antigen in the bloodstream of a mammalian subject, the method comprising:

Introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted protein antigen and a promoter operably linked to the nucleic acid molecule, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject, thereby inducing the immune response in the mammalian subject;

A method for reducing blood glucose levels in a hyperglycemic mammal, the method comprising introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a controlled release formulation or polymeric capsule that encapsulates a nucleic acid molecule encoding a secreted insulin protein, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the insulin protein from the cell and into the bloodstream of the subject in an amount effective to reduce blood glucose levels;

A method for reducing blood glucose levels in a hyperglycemic mammal, the method comprising introducing directly into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted insulin protein, wherein said construct is not packaged in a viral particle, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the insulin protein from the cell and into the bloodstream of the subject in an amount effective to reduce blood glucose levels;

does not reasonably provide enablement for the claimed invention as broadly claimed presently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With respect to the lack of sufficient description of the claimed "altered protein" relative to a wild-type protein for use in any oral gene therapy protocol as envisioned by applicants at the time the invention was made, as set forth in the above stated rejection, one skilled in the art would also not know how to make and use the claimed invention so that it would operate as intended. Furthermore, the problem of predicting protein structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any polypeptide sequence and finally what changes can be tolerated with respect thereto is complex and unpredictable (see Ngo et al., in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). This unpredictability is keyed on the fact that simple analysis of primary and secondary structures of a polypeptide is not well correlated with the ability of the

encoded DNA product to its functional activity because the relationship between the sequence of a polypeptide and its tertiary structure is not well understood and is not predictable; and, thus, it is not apparent how one skilled in the art arrives at all claimed nucleic acid sequences that exhibit a biological activity without undue experimentation, particularly given the lack of detailed guidance provided by the as-filed specification as to how to overcome the making of any altered protein so that it would retain its intended biological or therapeutic function.

NATURE OF INVENTION, GUIDANCE AND WORKING EXAMPLES

The application indicates that the present invention provides methods of treatment using gene therapy, more specifically gene therapy by expression of a DNA of interest in the GI tract (page 5, lines 7-25, and pages 6-9), and that the DNA of interest preferably encodes insulin, a growth hormone, clotting factor VIII, intrinsic factor, erythropoietin, factor IX, and all other blood factors (page 16 bridging page 19). Thus, it appears that the only disclosed method of use for the gene delivery through the bloodstream and expression of a polypeptide in the bloodstream is to have a therapeutic effect. Table 2 on pages 24-25 lists an enormous number of diseases including obesity, bone disease, allergic rhinitis, asthma, Addison's disease, spontaneous infertility, Vitiligo, arthritis, Polymyositis, Enzyme deficiency, cancer, and cardiovascular diseases that are compassed by the claimed gene therapy methods and pharmaceutical compositions. Note also that the claims also embrace the use of a DNA construct encoding a non-secretory protein and yet claiming that the expressed non-secretory protein, e.g., CFTR, can be transported extracellularly into the bloodstream. The application demonstrates that a direct injection of plasmid vectors expressing human insulin polypeptides into the GI tract of rats suffering from diabetes reduces blood glucose levels in treated rats (Example 4, Figure 7). Furthermore, Example 5 of the application provides data demonstrating that an injection of plasmid vectors expressing human growth hormones (hGH) via a catheter into the duodenum of the GI tract in rats allows expression of hGH in the bloodstream (Figure 11), wherein there is no therapeutic effect shown as the result of the hGH

expression. However, the specification does not teach or provide sufficient guidance for one skilled in the art to reasonably extrapolate, without undue experimentation, from the efficacy of plasmid vectors expressing human insulin in suppressing the diabetic syndrome in streptozotocin-treated rats to methods of treating all other diseases or disorders in any or all mammals, wherein DNA encoding any and all other therapeutic proteins and/or wherein any other administration route is employed.

THE STATE OF THE PRIOR ART, THE LACK OF A REASONABLE CORRELATION BETWEEN APPLICANT'S GUIDANCE AND WORKING EXAMPLES TO APPLICANT'S BREADTH OF THE PRESENTLY PENDING CLAIMS.

Major considerations for any gene transfer or gene therapy protocol involve issues that include:

- 1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;
- 2/ The type of vector and amount of DNA constructs to be administered;
- 3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site; and
- 4/ What amount is considered to be therapeutically effective for a gene therapy method (Coghlan, New Scientist, Vol. 148, pp. 14 and 15, 1995; Anderson, Nature, Vol. 392, 25-30, April 1998; and Gunzburg *et al.*, Vol. 1, No. 9, pages 410-417, 1995).

More specifically as to the unpredictability of gene therapy at the time the invention was made, Anderson summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph).

With regard to the use of liposome for administration *in vivo*, Ledley (Human Gene Ther. (1995)

6:1129-1144) teaches that "Many formulations that are effective *in vitro* fail to function *in vivo*...It is, in fact, not surprising that *in vitro* studies with gene delivery systems have not been predictive of *in vivo* functionality" (p. 1138, col. 1). Ledley also discloses several important biological constraints for *in vivo* nonviral gene delivery such as the bioavailability of the gene to the target cell, the physical chemistry of the cell surface, the rapid elimination of DNA from intravascular or interstitial compartments after administration, effects of the physicochemical properties of the administered complex *in vivo*, and the molecular biology of specific receptors and intracellular trafficking events (pp. 1138-39). More specifically, Ledley states that "it is unlikely that any one method for gene transfer will prove to be effective in every organ. Rather, various formulations will need to be developed that can be used to deliver DNA to specific targets based on the biological properties of that target" (p. 1139, col. 1).

Also see Abendroth, abstract, EMBASE, AN 96126219, 1996, and Ponder, abstract cited from MEDLINE, AN 200103902 as to the unpredictability of human gene therapy at the time the invention was made and even in 1999. Verma *et al.* (Nature, Vol. 389, 18, September 1997) also states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addressed" (page 239, column 3, first paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

Coghlan (New Scientist, November 1995) states that problems with gene therapy involve gene targeting and the number of genes reaching the target cells-estimated by some researchers to be about 1%. Coghlan discloses that even those genes which reach their destination work inefficiently, producing too little protein for too short a time period to benefit the patient. Neither the application nor the

incorporated references provide evidence showing that any and/or all pharmaceutical compositions other than the composition of an insulin encoded DNA would generate a therapeutic effect when employed in any of the disclosed gene therapy method. The evidences obtained from the working examples are not reasonably predictable and correlated to a therapeutic effect in any or all subjects using a genus of claimed pharmaceutical compositions as claimed. In fact, Ledley (Human Gene Ther. (1995) 6:1129-1144) teaches:

"it is unlikely that any one method for gene transfer will prove to be effective in every organ. Rather, various formulations will need to be developed that can be used to deliver DNA to specific targets based on the biological properties of that target" (p. 1139, col. 1). Furthermore, Wirtz *et al.* (GUT, 44, 6, pp. 800-807, 1999, abstract) teach that "intravenous or intraperitoneal injection of AdCMVbetaGal into healthy Balb/c mice caused strong reporter gene expression in the liver and spleen but not in the colon" (abstract).

Even with oral administration of immunogens and/or DNA vaccines, the state of the art exemplified by Cryz *et al.* (Vaccine, Vol. 14, 7, Vaccine Delivery Systems, Reports of the Expert Panels, pages 665-688, 1996) indicates that oral delivery of any vaccine to gastrointestinal cells, e.g., M cells, so as to have a therapeutic effect, remains unpredictable at the time the invention was made (page 674, columns 1 and 2). More specifically, Cryz *et al.* teach:

"Effective delivery to the GALT [gastrointestinal associated lymphoid tissue] is predicated with enormous problems. While it is a relatively simple task to deliver particles to certain sites in the intestine, the efficiency of uptake is very low. Recent studies suggest that less than a fraction of one percent of particles are taken up and translocated. Indeed recent studies in the UK failed to demonstrate the presence of fluorescent particles in M-cells of human subjects after repeated dosing with particulate carriers. Attempts have been made to improve the efficiency of the process by the use of particles carrying appropriate monoclonal antibodies or lectins but the results are not especially encouraging. The use of lipid vehicles could have some advantages. Not surprisingly, the gastrointestinal tract, because of its very nature, will be a less efficient site for particle uptake than other mucosal surfaces. The process of

presentation of a particle to M-cells is obviously a statistical problem. How does a particle in the centre of the lumen, carrying a receptor for M-cell interaction, 'know' that there are M-cells in the vicinity?" (page 674, column 2).

Furthermore, Doerfler *et al.* (Gene, 157/1-2, pp. 241-245, 1995, abstract) teach that when naked DNA is feed orally in mice, "a small amount of this DNA transiently survives the digestive regime of the animals' GI tract, although in a heavily fragmented form", and that "a minute proportion of the fed M13mp18 DNA can be retrieved from the bloodstream of mice between 2 and 8 h after feeding, mainly associated with the leukocyte population" (abstract).

Thus, it is not apparent how one skilled in the art determines, without undue experimentation, which of the genetic constructs or pharmaceutical compositions other than the insulin encoded DNA, and/or antigen encoding DNA for the purpose of inducing an immune response in the bloodstream of a mammal as disclosed in the as-filed application, would produce a therapeutic effect, particularly in view of the doubts expressed in the art of record at the time the invention was made.

While the specification demonstrates expressions of insulin pancreas of rats whereby glucose reduction was generated in the treated rats, it is not apparent whether such particular methods employing specific DNA constructs are reasonably extrapolated to any therapeutic effect by using any administration of any other protein encoded DNA in any human patient within the context of applicant's teaching (gene therapy see the entire specification), nor is it apparent how one skilled in the art extrapolates expression of hGH or insulin in rats to gene therapy methods using genetic constructs expressing therapeutic genes such as clotting factor VIII, erythropoietin, interferon-alpha 2b, interferon-alpha 2a, interleukin-2, interferon-alpha, adenosine deaminase, insulin-like growth factor-1, platelet-derived growth factor, and epidermal growth factor in a human patient within the context of intended therapeutic application of the gene therapy method as claimed. Note that a simple expression of growth factor IX in the bloodstream in mice, a simple expression of human growth hormone in rats, and an increase of blood cells (hematocrits) as a result of expression of human EPO in rats, all of which models employ direct retroductal injection of naked plasmid encoding respective proteins, are not the same as claiming an oral route of introduction of

any DNA encoding any therapeutic into the GI tract in any mammal including a human patient so as to provide a therapeutically relevant effect, nor is it the same as a therapeutic effect within the context of the teachings provided by the as-filed specification. Neither the working murine or rat models can be considered as a general observed phenomenon so as to reasonably extrapolated to any human gene therapy to treat any human disease or disorder as presently claimed, particularly on the basis of applicant's disclosure and given the doubts expressed in the art of record and the sufficient reasons set forth in the stated rejection.

Thus, in view of the lack of guidance regarding the subject matter of the claims within the context of human gene therapy of using any therapeutic DNA for treatment of any disease or disorder through hepatic route of DNA delivery, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention as claimed.

With respect to the breadth of the base claim that embrace the making and use of a non-secretory protein encoded DNA sequence that must exhibit the ability to be transported extracellularly into the bloodstream from a transfected intestinal epithelial cell, the as-filed specification does not provide any guidance as to how such contemplated property can be accomplished with a DNA encoding a non-secretory protein. As such, the as-filed specification only provides a reasonable enablement for claims readable the making of a DNA construct encoding a secretory protein, which exhibits the ability to be transported extracellularly into the bloodstream due the presence of a signal sequence in the coding region of the protein.

Note also that the specification fails to teach any specific targeting techniques, fails to provide sufficient guidance and/or factual evidence to demonstrate any vector targeting other than *in vivo* direct injection of a DNA construct expressing an insulin gene product so as to generate a therapeutic effect, and fails to direct the skilled artisan to any teachings of targeting strategies and of using vector constructs other than injection of the insulin expressing constructs into the GI tract of a subject which would allow

one of skill in the art to practice the full scope of the claimed invention without undue experimentation, particularly in view of the doubts expressed in the art of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in—

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 18-25, 27, 30-33 and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Mathiowitz *et al.* (US Pat No. 6,248,720 B1).

The claims are readable on a method of orally delivering a secreted protein antigen or an insulin protein in the bloodstream of a mammalian subject, the method comprising:

Introducing into the gastrointestinal tract of a mammalian subject by an oral administration of a construct comprising a nucleic acid molecule encoding a secreted protein antigen or an insulin protein, wherein said construct is encapsulated by a polymeric microcapsule, which is produced by phase inverson microencapsulation, said introducing resulting in introduction of the construct into an intestinal epithelial cell and secretion of the protein from the cell and into the bloodstream of the subject.

Mathiowitz *et al.* teach an identical method of orally delivering any mucosal epithelial surface, which includes the mucosal epithelial surface of the GI tract, of a DNA encoding an antigen or an insulin protein to a mammal, wherein the DNA is encapsulated in a polymeric capsule, *e.g.*, see claim 8 of the patent, columns 18-19. Column 20 discloses a number of agents that can be used to protect the DNA from degradation in the stomach. Columns 16 and 17 disclose that the DNA encodes an antigen or an insulin protein. Column 4 states that microcapsules are used interchangeably with microparticles and microspheres.

Note that the essential features of the claimed systems and/or compositions are that as long as a vector comprising a DNA of interest operably linked to a promoter is formulated in a composition suitable for *in vivo* administration, *e.g.*, a pharmaceutically acceptable carrier including a buffered solution, the non-viral vector would be able to function as intended, *e.g.*, delivery of any coding DNA and its subsequent expression and secretion into the bloodstream. The specification as a whole (pages 10-17, for example) clearly indicates:

"Any nucleic acid vector having a eukaryotic promoter operably linked to a DNA of interest can be used in the invention to transform a secretory gland cell" (page 10, last paragraph); and

"The DNA of interest can be any DNA sequence encoding any protein or other gene product" (page 18, first paragraph).

Absent evidence to the contrary, the protein encoded by the DNA construct of Mathiowitz is delivered to the mucosal surface composed of epithelial intestinal cells, is expressed in the cells, and is released subsequently into the bloodstream of a treated mammal.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-25, 27 29-33 and 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,258,789, or claims 1-8 of US patent No. 6,225,290B1

Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims embrace the claims from the issued patents and thus, the examined claims are anticipated by the claims from the issued patents. Note that the term "construct" as claimed in the US patents, when read in light of the as-field specification, is defined as embracing capsules and/or controlled release formulations that protect the degradation of the nucleic acid sequence as recited in the claims during its delivery through an oral route into intestinal epithelial cells.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051**.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632



**DAVE T. NGUYEN
PRIMARY EXAMINER**